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Original Article

Exploring the Potential Factors Affecting the Type of Pathogens Responsible for Urinary Tract Infection in Neonatal Hyperbilirubinemia

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Abstract

Background: Unexplained neonatal hyperbilirubinemia may be the sole clinical presentation of urinary tract infection (UTI) in newborns. We aimed to determine the potential factors affecting the type of pathogens responsible for UTI in neonatal hyperbilirubinemia.

Methods: This cross-sectional study retrospectively evaluated newborns admitted to the neonatal ward of Bandar Abbas Children's Hospital between 2016 and 2018. Newborns with hyperbilirubinemia and culture-confirmed UTIs were included in the study. The following data were extracted from patients' medical records: demographics and anthropometrics, type of delivery, newborn feeding, clinical manifestations, urine sampling method, and laboratory test results, including total bilirubin and urine culture.

Results: Of the 96 neonates with hyperbilirubinemia and positive urine culture in this study, 63 (65.6%) were male. Their mean age was 13.60 ± 6.00 days. *Escherichia coli* was the most common pathogen isolated from the urine cultures (33.3%), followed by *Klebsiella* (24%). Age, gender, gestational age, birth weight, type of delivery, newborn feeding, clinical manifestations, total bilirubin level, and urine sampling method were not associated with the type of pathogens isolated from urine culture ($P > 0.05$).

Conclusion: Most urine cultures from newborns with hyperbilirubinemia were positive for *E. coli*. None of the potential factors evaluated in this study were correlated with the type of pathogens responsible for UTI in neonates with hyperbilirubinemia.

Keywords: Hyperbilirubinemia, Neonates, Urinary tract infection, Urine culture

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Background

Hyperbilirubinemia is common in newborns. Total serum bilirubin may not surpass physiological values in some neonates, but it may do so in others, at which it requires treatment. During the regular evaluation of newborns with significant hyperbilirubinemia, several well-known causes might be identified, while others may go unnoticed (1). On the other hand, because of their immature immune systems, newborns are more likely to develop urinary tract infections (UTIs) in their first few months of life (2, 3). Although fever is a significant indicator of UTI in newborns, a considerable percentage of neonatal UTIs do not manifest with a fever or particular urinary tract symptoms. As a result, understanding non-specific signs and symptoms of newborn UTI is critical for identifying relevant cases that need an early diagnosis to avoid long-term complications (2).

In the absence of additional symptoms or indications, unexplained neonatal hyperbilirubinemia may be the sole clinical presentation of UTI in newborns (4, 5). The American Academy of Pediatrics (AAP) guidelines advocate urinalysis and urine culture in infants with conjugated hyperbilirubinemia (6). Furthermore, unconjugated hyperbilirubinemia may be a significant or the earliest manifestation of UTI (7, 8). Additionally, recent systematic reviews have evaluated the incidence of UTI in newborns with persistent jaundice (9, 10). Potentially, the direct effect of the UTI microorganisms on the structures and cells responsible for the secretion of conjugated bilirubin causes jaundice (11). It is possible

that some factors may affect or determine the UTI-causing pathogens when neonates have concomitant hyperbilirubinemia; however, these factors have not been explored in previous studies. This study aimed to determine the potential factors influencing the type of pathogens responsible for UTI in neonatal hyperbilirubinemia.

Materials and Methods

Participants and Study Design

This cross-sectional study retrospectively evaluated newborns admitted to the neonatal ward of Bandar Abbas Children's Hospital between 2016 and 2018. The participants' informed consent was not required because of the retrospective nature of this research. The inclusion criteria were hyperbilirubinemia and positive urine culture. Urine cultures on catheterized samples $\geq 10^5$ and those on suprapubic ones with one-colony-forming unit were considered positive. Newborns with urinary tract anomalies were excluded from the study. Of the 683 evaluated medical records, 96 met the inclusion criteria.

The following data were extracted from the patients' medical files:

- Demographics and anthropometrics: age, gender, gestational age, and birth weight
- Type of delivery: cesarean section (C-section) or normal vaginal delivery (NVD)
- Newborn's feeding: breastfeeding or formula feeding
- Clinical manifestations: fever, poor feeding, and hyporeflexia
- Urine sampling method: suprapubic aspiration or catheterization
- Laboratory test results: total bilirubin and urine culture

Data Analysis

SPSS version 25.0 was used for data analysis. Mean, standard deviation, frequency, and percentage were used to describe the variables. The one-way analysis of variance (ANOVA) test was used to compare continuous variables between groups. The chi-squared and Fisher's exact tests were used to compare categorical variables. P values ≤ 0.05 were considered significant in all statistical tests.

Results

Of the 96 neonates with hyperbilirubinemia and positive urine culture in this study, 63 (65.6%) were male and 33 (34.4%) were female. Their mean age was 13.60 ± 6.00 days. Most were born by C-section (61.5%) and received breastfeeding (93.8%). Fever, poor feeding, and hyporeflexia were present in 1%, 3.1%, and 2.1% of the newborns, respectively. Urine samples were mostly obtained by the suprapubic aspiration (85.4%). *Escherichia coli* was the most common pathogen isolated from the urine cultures (33.3%), followed by *Klebsiella* (24%) (Table 1).

Age, gender, gestational age, birth weight, type of delivery, newborn feeding, clinical manifestations, total bilirubin level, and urine sampling method were not associated with the type of pathogens isolated from urine culture ($P > 0.05$) (Table 2).

Discussion

In this study, *E. coli* and *Klebsiella* were the most common microorganisms responsible for UTI in neonates with hyperbilirubinemia, which is in line with the findings of previous studies (10, 12-15). It has been suggested that jaundice associated with UTI may be caused by *E. coli* or other Gram-negative organisms hemolyzing the blood, which might lead to unconjugated hyperbilirubinemia (16). Moreover, we found that newborn feeding was not associated with the type of pathogens isolated from urine culture. In contrast, Hosseini et al found that formula-fed infants were more likely to have concomitant hyperbilirubinemia and UTI (17), while they did not

Table 1. General Characteristics of the Study Participants

Variables	Values
Age (days), mean (SD)	13.60 (6.00)
Gender, No. (%)	
Male	63 (65.6)
Female	33 (34.4)
GA (wk), mean (SD)	38.27 (2.09)
Birth weight (g), mean (SD)	3059.07 (506.32)
Type of delivery, No. (%)	
NVD	37 (38.5)
C-section	59 (61.5)
Newborn feeding, No. (%)	
Breastfeeding	90 (93.8)
Formula feeding	3 (3.1)
Breastfeeding and formula feeding	3 (3.1)
Clinical manifestations, No. (%)	
Fever	1 (1.0)
Poor feeding	3 (3.1)
Hyporeflexia	2 (2.1)
Total bilirubin (mg/dL), mean (SD)	11.65 (5.39)
Urine sampling method, No. (%)	
Suprapubic aspiration	82 (85.4)
Catheterization	14 (14.6)
Urine culture results, No. (%)	
Escherichia coli	32 (33.3)
Klebsiella	23 (24.0)
Citrobacter	5 (5.2)
Enterobacter	11 (11.5)
Others	25 (26.0)

Abbreviations: N: number; SD: standard deviation; GA: gestational age; NVD: normal vaginal delivery; C-section: cesarean section.

Table 2. The Correlation of the Type of Bacteria Isolated from Urine Cultures with Hyperbilirubinemia and Other Factors

Variables	*Escherichia coli*	*Klebsiella*	*Citrobacter*	*Enterobacter*	Others	*P* Value
Age (days), mean (SD)	13.78 (6.30)	13.82 (6.31)	12.60 (7.10)	12.54 (4.94)	13.84 (5.50)	0.449
Gender, No. (%)						
Male	23 (71.9)	13 (56.5)	3 (60.0)	8 (72.7)	16 (64.0)	0.783
Female	9 (28.1)	10 (43.5)	2 (40.0)	3 (27.3)	9 (36.0)	
GA (weeks), mean (SD)	38.50 (2.39)	37.90 (2.33)	38.00 (2.54)	38.00 (1.57)	38.50 (1.47)	0.461
Birth weight (g), mean (SD)	3081.00 (567.60)	2942.10 (502.30)	2956.00 (562.80)	3220.00 (477.80)	3088.40 (421.30)	0.466
Type of delivery, No. (%)						
NVD	17 (53.1)	7 (30.4)	1 (20.0)	2 (18.2)	10 (40.0)	0.186
C-section	15 (46.9)	16 (69.6)	4 (80.0)	9 (81.8)	15 (60.0)	
Newborn feeding, No. (%)						
Breastfeeding	30 (93.8)	22 (65.7)	4 (80.0)	10 (90.9)	24 (96.0)	0.423
Formula feeding	1 (3.1)	0 (0.0)	0 (0.0)	1 (9.1)	1 (4.0)	
Breastfeeding and formula feeding	1 (3.1)	1 (4.3)	1 (20.0)	0 (0.0)	0 (0.0)	
Clinical manifestations, No. (%)						
Fever	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.732
Poor feeding	1 (3.1)	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.451
Hyporeflexia	0 (0.0)	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.166
Total bilirubin (mg/dL), mean (SD)	10.87 (5.06)	12.86 (5.70)	9.40 (5.36)	12.00 (3.88)	11.84 (5.72)	0.850
Urine sampling method, No. (%)						
Suprapubic aspiration	29 (90.6)	20 (87.0)	4 (80.0)	9 (81.8)	20 (80.0)	0.816
Catheterization	3 (9.4)	3 (13.0)	1 (20.0)	2 (18.2)	5 (20.0)	

Abbreviations: N: number; SD: standard deviation; GA: gestational age; NVD: normal vaginal delivery; C-section: cesarean section.
[a] Analyzed by the ANOVA/ANCOVA test.
[b] Calculated using Cohen's d.

explore the potential correlation of neonatal feeding with the type of pathogens responsible for UTI. This discrepancy may be attributable to the small number of newborns in our sample who received formula. On the other hand, there was no correlation between gender and type of pathogens in this study, which is in line with the findings of Hosseini et al (17).

Furthermore, gestational age, neonate's age, birth weight, and total bilirubin levels were not linked to the type of urinary pathogens in our research. Besides, the delivery type was not associated with the isolated bacteria. These findings are consistent with those of the study by Hosseini et al (17). However, Rashed et al demonstrated different results (18). This discrepancy may be brought about by variations in maternal communicable infections or the difference in the quality of delivery in terms of hygiene between studies.

In the current study, clinical manifestations including fever, poor feeding, and hyporeflexia were not associated with the type of the responsible pathogen. These presentations may occur after a variety of illnesses caused by various bacteria and may represent infection-related unspecific consequences. Therefore, it would have been expected that there would be no link in this area.

As a common condition in newborns, hyperbilirubinemia is often benign and resolves spontaneously. About 60% of term and 80% of preterm neonates suffer from hyperbilirubinemia during the first week of life. A major cause of neonatal hyperbilirubinemia is physiologic jaundice. The diagnosis is determined after ruling out other significant causes such as hemolysis, infection, and metabolic disorders (19). Prolonged jaundice is defined as hyperbilirubinemia that persists beyond two weeks. Hemolysis, congenital glucuronyl transferase deficiency, hypothyroidism, bowel obstruction, metabolic diseases including galactosemia, and UTI may all result in prolonged unconjugated hyperbilirubinemia. Due to frequent phototherapy sessions and multiple blood samples taken from the newborn, prolonged icterus may be quite stressful for the parents (19).

The major limitation of the current study was its relatively small sample size. The sample size for each pathogen from urine culture was not sufficient for the comparison of some variables, and *P*-values are largely dependent on sample size.

Conclusion

Escherichia coli was detected in the majority of urine cultures from neonates with hyperbilirubinemia. The bacteria that cause UTI in newborns with hyperbilirubinemia were not associated with any of the relevant variables examined in this investigation. To ascertain the genuine association of

the causative microorganisms with various parameters as well as their possible relationship with the occurrence of hyperbilirubinemia, large case-control studies including neonates with UTI and without hyperbilirubinemia may be beneficial.

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Competing Interests
The authors declare that they have no competing interests.

Ethical Approval
The research adheres to the principles of the Declaration of Helsinki and was given ethical clearance by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1400.208). The participants' informed consent was not required because of the retrospective nature of this research.

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